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Health Effects Assessment for Dichlorobenzenes

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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with dichlorobenzenes. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Dichlorobenzenes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-039. NTIS PB81-117509.

U.S. EPA. 1983a. Reportable Quantity Document for 1,2-Dichlorobenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1983b. Reportable Quantity Document for 1,4-Dichlorobenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985. Health Assessment Document for Chlorinated Benzenes. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-84-015F. NTIS PB85-150332.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan).

This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

An RfD_{SI} of 31 mg/day and an RfD_I of 3.1 mg/day were derived for 1,2-dichlorobenzene based on a NOAEL in rats of 44.2 mg/kg/day associated with 49 ppm (290 mg/m³) 7 hours/day, 5 days/week for 7 months (Hollingsworth et al., 1958). Higher concentrations were associated with decreased body weights. An RfD_{SO} of 63 mg/day was based on a NOAEL in rats of 125 mg/kg, 5 days/week in a 13-week gavage study (NTP, 1985). An interim RfD_O of 30 mg/day was based on a NOAEL of 60 mg/kg, 5 days/week in a 103-week gavage study using rats (NTP, 1985). Higher doses were associated with mild degenerative lesions in the liver. Male mice treated with 1,2-dichlorobenzene developed mild kidney tubular degeneration followed by regeneration (NTP, 1985). A CS of 9 was calculated for this effect in a 103-week gavage study (NTP, 1985).

Data were not sufficient to permit quantitative risk assessment for 1,3-dichlorobenzene. Following the lead of U.S. EPA (1985b), risk assessment was not performed for 1,3-dichlorobenzene by analogy to the other isomers.

1,4-Dichlorobenzene has been shown to be carcinogenic to rats and mice when given chronically by gavage (NTP, 1986), but not when given chronically by inhalation (Loeser and Litchfield, 1983). In the gavage study, male and female mice had an increased incidence of liver tumors and male rats had an increased incidence of kidney tumors. A q_1^* of 2.4×10^{-2} mg/kg based on the incidence of liver tumors in male mice was chosen as an estimate of the carcinogenic potential of 1,4-dichlorobenzene to humans.

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LIST OF ABBREVIATIONS

AADI	Adjusted acceptable daily intake
ADI	Acceptable daily intake
BUN	Blood urea nitrogen
CAS	Chemical Abstract Service
CS	Composite score
DCB	Dichlorobenzene
GGTP	γ-Glutamyl transpeptidase
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RMCL	Recommended maximum contaminant level
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SGPT	Serum glutamic pyruvic transaminase

LIST OF ABBREVIATIONS (cont.)

SNARL	Suggested no adverse response level
STEL	Short-term exposed level
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected chemical and physical properties and environmental fate of 1,2-dichlorobenzene, 1,3-dichlorobenzene and 1,4-dichlorobenzene are listed in Table 1-1.

In the atmosphere, the dichlorobenzene isomers should exist primarily in the vapor phase and are expected to react with photochemically generated hydroxyl radicals. The atmospheric half-lives listed in Table 1-1 were calculated using observed rate constants of 0.42×10^{-12}, 0.72×10^{-12} and 0.32×10^{-12} cm^3/molecule-sec at 22°C for 1,2-, 1,3- and 1,4-dichlorobenzene, respectively (Atkinson, 1985), and an ambient hydroxyl radical concentration of 8.0×10^5 molecules/cm^3. The detection of each of the dichlorobenzene isomers in rainwater (Pankow et al., 1984) suggests that atmospheric removal through washout is also possible.

In water, adsorption to sediments will be a major fate process based upon extensive monitoring data in the Great Lakes area and K_{oc} values derived from these experimental data (Oliver and Nicol, 1982; Oliver 1983; Oliver and Charlton, 1984). Analysis of Lake Ontario sediment cores has indicated the presence and persistence of 1,2-, 1,3- and 1,4-dichlorobenzene (Oliver and Nicol, 1982). The dichlorobenzenes may volatilize from the water column; the estimated half-life for volatilization from a river 1 m deep flowing at a speed of 1 m/sec with a wind velocity of 3 m/sec is ~4 hours for each of the dichlorobenzenes (Lyman et al., 1982). Adsorption to sediments will greatly reduce volatilization.

The half-lives of the dichlorobenzene isomers in soil could not be located in the available literature. The wide range in K_{oc} values indicates that the dichlorobenzenes can be moderately to tightly adsorbed to

TABLE 1-1

Selected Chemical and Physical Properties and Environmental Fate of the Dichlorobenzenes

Property	1,2-Dichlorobenzene	1,3-Dichlorobenzene	1,4-Dichlorobenzene	Reference
CAS number:	95-50-1	541-73-1	106-46-7	
Chemical class:	haloaromatic compound	haloaromatic compound	haloaromatic compound	
Molecular weight:	147.0	147.0	147.0	
Vapor pressure at 25°C:	1.5 mm Hg	1.5 mm Hg	0.75 mm Hg	Weber et al., 1981
Water solubility at 25°C:	154 mg/ℓ	134 mg/ℓ	137 mg/ℓ	Chiou et al., 1983
Log octanol/water partition coefficient:	3.38	3.60	3.52	Hansch and Leo, 1985
Bioaccumulation factor:	270-560, rainbow trout (Salmo gairdneri) 66, bluegill sunfish (Lepomis macrochirus)	420-740, rainbow trout (Salmo gairdneri) 89, bluegill sunfish (Lepomis macrochirus)	370-720, rainbow trout (Salmo gairdneri) 60, bluegill sunfish (Lepomis macrochirus)	Oliver and Niimi, 1983; Barrows et al., 1978
Soil adsorption coefficient:	280-320, silt loam soil; 39,800, suspended sediments	293, silt loam soil; 12,600-31,600 suspended sediments	273, silt loam soil 63,000-100,000 suspended sediments	Chiou et al., 1979, 1983; Lewis et al., 1985
Half-lives in Air:	24 days (estimated)	14 days (estimated)	31 days (estimated)	Atkinson, 1985
Water:	4 hours, unadsorbed form (estimated); years, adsorbed form	4 hours, unadsorbed form (estimated); years, adsorbed form	4 hours, unadsorbed form (estimated); years, adsorbed form	Lyman et al., 1982; Oliver and Nicol, 1982
Soil:	NA	NA	NA	

NA = Not available

soil (Swann et al., 1984). The detection of these compounds in groundwaters indicates that leaching can occur under certain conditions (Page, 1981; Hutchins et al., 1983). Based on the vapor pressure of the dichlorobenzenes, volatilization from soil surfaces may be an important transport mechanism, although volatilization may be reduced by adsorption or leaching. It is possible that slow biodegradation in soil under aerobic condtions will occur (Haider et al., 1974).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

In reviews on chlorinated benzenes, Ware and West (1977) and U.S. EPA (1985a) concluded that all three isomers (1,2-, 1,3- and 1,4-dichlorobenzene) are absorbed through the gastrointestinal tracts of humans and experimental animals.

Quantitative data on the absorption of 1,2- or 1,3-dichlorobenzene after oral exposure could not be located in the available literature.

Experimental excretion data indicate that most of the orally administered 1,4-dichlorobenzene is absorbed from the gastrointestinal tract (Hawkins et al., 1980). Two female CFY (Sprague-Dawley derived) adult rats weighing ~200 g were treated by gavage with 250 mg/kg/day of radioactive ^{14}C-1,4-dichlorobenzene in sunflower oil for 10 days (Hawkins et al., 1980). Recovery of radioactivity equivalent to 1.6 mg of 1,4-dichlorobenzene from the feces 5 days after termination of the treatment indicated that 1,4-dichlorobenzene was almost completely absorbed from the gastrointestinal tract. In bile duct cannulated rats, the recovery of 9% of the administered radioactivity from the feces within 24 hours of treatment is further evidence that gastrointestinal absorption is >90%. Peak levels of radioactivity in plasma at 2-4 hours following the last of 10 daily gavage doses indicate the rapidity of gastrointestinal absorption.

2.2. INHALATION

In reviews of chlorinated benzenes, Ware and West (1977) and U.S. EPA (1985a) concluded that all three isomers (1,2-, 1,3- and 1,4-dichlorobenzene) of dichlorobenzene are absorbed by the lungs of humans and experimental animals.

Quantitative data on the absorption of 1,2- or 1,3-dichlorobenzene after inhalation exposure could not be located in the available literature. Experimental data indicate, however, that a substantial amount of the administered 1,4-dichlorobenzene is absorbed in rats after inhalation (Hawkins et al., 1980). Two female CFY (Sprague-Dawley derived) rats were exposed to 1000 ppm of radioactive ^{14}C-1,4-dichlorobenzene for 3 hours/day for up to 10 days. Recovery of radioactivity equivalent to 53.5 mg of 1,4-dichlorobenzene from the urine and feces, collectively, within 5 days after termination of the treatment, indicated that substantial 1,4-dichlorobenzene had been absorbed by the lungs, although a more quantitative estimate cannot be made from these data.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Groups of 10 male and 10 female B6C3F1 mice and 10 male and 10 female F344/N rats were treated by gavage with 0, 30, 60, 125, 250 or 500 mg/kg/day of 1,2-dichlorobenzene in corn oil 5 days/week for 13 weeks (NTP, 1985). Parameters evaluated included mortality, body and organ weights, clinical chemistry (in rats only), hematology and histology. Decreased spleen-to-body weight ratios unaccompanied by histological changes were observed in female mice at all dose levels tested. Liver necrosis was observed in the male mice but not the females treated with 250 mg/kg/day. Increased mortality, decreased body weight, increased liver weight accompanied by hepatocellular degeneration and necrosis, lymphoid depletion in the spleen and thymus and an increased incidence of heart and skeletal muscle lesions were observed in male and female mice treated with 500 mg/kg/day.

Dose-related increases in liver weight accompanied by hepatocellular necrosis were observed in rats treated with 250 or 500 mg/kg/day of 1,2-dichlorobenzene. Although relative liver weight was significantly increased in male and female rats treated with 125 mg/kg/day, the histological changes observed at 125 mg/kg/day were less pronounced than those at higher dose levels and occurred in 1 of 10 male rats and 2 or 3 of 10 female rats. The male rat with focal hepatic necrosis died early because of a gavage error. Although no effects on serum levels of SGPT, GGTP or alkaline phosphatase were observed, "slight" dose-related increases in the serum levels of cholesterol (30 and $\geq$125 mg/kg/day in males; $\geq$125 mg/kg/day in females), triglycerides (500 mg/kg/day in males; 250 mg/kg/day in females) and total protein ($\geq$250 mg/kg/day in males; $\geq$30 mg/kg/day in

females) were reported. In rats treated with 500 mg/kg/day of 1,2-dichlorobenzene, slightly decreased hemoglobin and hematocrit levels and thymic and splenic lymphoid depletion occurred in both sexes, increased kidney weight accompanied by renal tubular degeneration occurred in males and decreased survival occurred in females.

The results of the NCI bioassay (NTP, 1985) support the earlier study of Hollingsworth et al. (1958) in which groups of 10 white female rats were treated by gavage with 0, 18.8, 188 or 376 mg/kg/day of 1,2 dichlorobenzene (>99% purity) in olive oil 5 days/week for a total of 138 treatments in 192 days. Increased liver and kidney weights were observed in rats treated with 188 or 376 mg/kg/day of 1,2-dichlorobenzene. The increased liver weight was accompanied by cloudy swelling in rats treated with 376 mg/kg/day of 1,2-dichlorobenzene. No adverse effects were observed in the rats treated with 18.8 mg/kg/day of 1,2-dichlorobenzene.

Pertinent data regarding the systemic toxicity of 1,3-dichlorobenzene after subchronic oral exposure could not be located in the available literature.

The NTP (1986) performed two subchronic oral studies with 1,4-dichlorobenzene in B6C3F1 mice. In the first 13-week study, groups of 10 male and 10 female B6C3F1 mice were treated by gavage with 0, 600, 900, 1000, 1500 or 1800 mg/kg/day of 1,4-dichlorobenzene in corn oil 5 days/week. Endpoints evaluated included mortality, body and organ weight, hematology clinical chemistry urinalysis and histology of the major organs. Body weight was significantly depressed and the incidence of hepatocellular degeneration significantly increased in male and female mice at all dose levels tested. In addition, there was a significant decrease in the number of white blood cells in male mice at all dose levels tested and in female mice only at 1000

and 1500 mg/kg/day. Mortality was significantly increased in male mice treated with 1000 mg/kg/day of 1,4-dichlorobenzene and in male and female mice treated with ≥1500 mg/kg/day. No effect was observed on hematocrit or SGPT levels. In the second 13-week study, groups of 10 male and 10 female B6C3F1 mice were treated by gavage with 0, 84.4, 168.8, 337.5, 675 or 900 mg/kg/day of 1,4-dichlorobenzene in corn oil 5 days/week. Endpoints evaluated included mortality rate, body weight and histology; no effects were reported on mortality or body weight. The incidence of centrilobular hepatocytomegaly was significantly increased in both male and female mice treated with 675 or 900 mg/kg/day of 1,4-dichlorobenzene. No adverse hepatic effects were observed in mice of either sex treated with ≤337.5 mg/kg/day of 1,4-dichlorobenzene.

The NTP (1986) also performed two subchronic oral studies with 1,4-dichlorobenzene in F344 rats. In the first 13-week study, groups of 10 male and 10 female F344 rats were treated by gavage with 0, 300, 600, 900, 1200 or 1500 mg/kg/day of 1,4-dichlorobenzene in corn oil 5 days/week. Endpoints evaluated include mortality, body and organ weight, hematology, clinical chemistry, urinalysis and histology of the major organs. Decreased survival occurred in males receiving 1200 or 1500 mg/kg/day and in females receiving 1500 mg/kg/day. Decreased weight gain was observed in the male rats at all dose levels tested but in the female rats only at 1200 and 1500 mg/kg/day. Liver-to-brain weight ratios were increased in both male and female rats treated with ≥900 mg/kg/day of 1,4-dichlorobenzene; kidney-to-brain weight ratios were increased only in male rats treated with ≥600 mg/kg/day. Hematological changes (decreased hematocrit, red blood cell count and hemoglobin levels and increased number of reticulocytes) occurred in male rats at all dose levels tested, but not females. No changes in SGPT levels

were reported, but BUN levels were significantly increased in male rats treated with ≥900 mg/kg/day. Renal tubular degeneration was observed at all dose levels tested in male rats but not in female rats. Hepatocellular degeneration, bone marrow hypoplasia and lymphoid depletion in the spleen and thymus were observed in male and female rats treated with 1200 or 1500 mg/kg/day.

In the second 13-week study, groups of 10 male and 10 female F344 rats were treated by gavage with 0, 37.5, 75, 150, 300 or 600 mg/kg/day of 1,4-dichlorobenzene in corn oil 5 days/week. Endpoints evaluated included mortality rate, body weight and histology. No compound-related deaths occurred and there was no effect on the body weight gain of rats of either sex treated with 1,4-dichlorobenzene. Dose-related increases in the intensity of renal tubular degeneration occurred in male rats treated with ≥150 mg/kg/day. Mild renal tubular degeneration was reported in 7/10 vehicle control male rats; mild to moderate renal tubular degeneration in 5/10 male rats treated with 150 mg/kg/day; moderate renal tubular degeneration in 3/10 male rats treated with 300 mg/kg/day; and moderate renal tubular degeneration in 9/10 male rats treated with 600 mg/kg/day of 1,4-dichlorobenzene.

Groups of 10 white female rats were treated by gavage with 0, 18.8, 188 or 376 mg/kg/day of 1,4-dichlorobenzene in olive oil 5 days/week for a total of 138 treatments in 192 days (Hollingsworth et al., 1956). Increased kidney and liver weights were observed in rats treated with 188 mg/kg/day. The increased liver weight was accompanied by cirrhosis and focal necrosis in rats treated with 376 mg/kg/day. No adverse effects were observed in the rats treated with 18.8 mg/kg/day.

3.1.2. Inhalation. Groups of 7-8 male and 7-8 female guinea pigs and 16-20 male and 17-20 female rats were exposed to 0, 49 ppm (290 mg/m³) or 93 ppm (560 mg/m³) of 1,2-dichlorobenzene, 7 hours/day, 5 days/week for up to 7 months (Hollingsworth et al., 1958). The only effect reported in guinea pigs was decreased spleen weight unaccompanied by any histological alteration in the males exposed to 560 mg/m³. In rats, the only effect reported was significantly depressed body weight in the males exposed to 560 mg/m³. No effects were reported in rats or guinea pigs exposed to 290 mg/m³ of 1,2-dichlorobenzene. In addition, no adverse effects were observed in two male and two female rabbits and two female monkeys exposed to 560 mg/m³ by the same protocol.

Pertinent data regarding the systemic toxicity of subchronic inhalation of 1,3-dichlorobenzene could not be located in the available literature.

Groups of 10-20 male and 10-20 female rats and 8-10 male and 8-10 female guinea pigs were exposed to 0, 96 ppm (580 mg/m³), 158 ppm (950 mg/m³) or 341 ppm (2050 mg/m³) of 1,4-dichlorobenzene, 7 hours/day, 5 days/ week for up to 7 months (Hollingsworth et al., 1956). At $\geq$950 mg/m³, adverse effects were observed in the livers of rats and decreased growth was observed in the guinea pigs. No adverse effects were observed in rats or guinea pigs exposed to 580 mg/m³. In addition, 10 female mice, 1 female monkey and 1 rabbit of each sex that were exposed to 580 mg/m³ of 1,4-dichlorobenzene for 7 hours/day, 5 days/week for 6-7 months had no adverse effects associated with 1,4-dichlorobenzene exposure.

3.2. CHRONIC

3.2.1. Oral. In groups of 50 male and 50 female B6C3F1 mice treated by gavage with 0, 60 or 120 mg/kg/day of 1,2-dichlorobenzene in corn oil, 5 days/week for 103 weeks and killed 2 weeks later, there was a dose related

increase in the incidence of renal tubular regeneration in males (NTP, 1985). Renal tubular regeneration occurred in 8/48 mice in the control group, 12/50 in the low-dose group and 17/49 in the high-dose group (p=0.035, Fisher Exact Test). No other adverse effects were reported.

Treatment by gavage of groups of 50 male and 50 female F344 rats with 0, 60 or 120 mg/kg/day of 1,2-dichlorobenzene in corn oil 5 days/week for 103 weeks resulted in no observed adverse effects on survival, body weight or the histology of any organ including the liver, kidney, bone marrow and spleen (NTP, 1985). Gavage errors appear to be responsible for decreased survival observed in the high-dose male rats.

Pertinent data regarding the toxicity of chronic oral exposure to 1,3-dichlorobenzene could not be located in the available literature.

Groups of 50 male and 50 female B6C3F1 mice were treated by gavage with 0, 300 or 600 mg/kg/day of 1,4-dichlorobenzene in corn oil 5 days/week for 103 weeks and killed ~2 weeks after the last treatment (NTP, 1986). Endpoints evaluated included mortality rate, body weight and histology of major organs. No effects were observed on the mortality rate or body weight of either sex. Nonneoplastic lesions occurred in the livers and kidneys of both male and female mice. Although more prevalent in the male mice, hepatocellular degeneration, cell size alteration and focal necrosis were significantly increased in both males and females at both dose levels evaluated. Degeneration of the renal tubular epithelium occurred in both male and female mice at both dose levels evaluated. The incidence, however, was higher in the male mice. Renal tubular regeneration was also observed in the female mice but not in the male mice. Adrenal medullary and capsular hyperplasia and thyroid follicular cell hyperplasia occurred in a dose-related manner in male mice but not females.

Groups of 50 male F344 rats were treated by gavage with 0, 150 or 300 mg/kg/day of 1,4-dichlorobenzene and groups of 50 female F344 rats were treated by gavage with 0, 300 or 600 mg/kg/day of 1,4-dichlorobenzene, in corn oil, 5 days/week for 103 weeks and killed ~1 week after the last treatment (NTP, 1986). Endpoints evaluated included mortality rate, body weight and histology of major organs. The mortality rate was significantly increased in the high-dose males. Mean body weight of the high-dose female rats was 5-7% lower than the control value. 1,4-Dichlorobenzene increased the incidence of nonneoplastic nephropathy, characterized by renal tubular atrophy, degeneration and regeneration, tubular dilation, thickening of the basement membrane, minimal accumulation of interstitial collagen and the presence of granular casts in dosed female rats (control 21/49; low 32/50; high 41/49), but not in male rats where the incidence of nephropathy was equally high in all three groups (control 42/50; low 42/50; high 46/50). Renal pelvic epithelial cell and tubular cell hyperplasia, as well as parathyroid hyperplasia, occurred in a dose-related manner in male rats but not females.

3.2.2. Inhalation. Pertinent data regarding the toxicity of chronic inhalation of 1,2- or 1,3-dichlorobenzene could not be located in the available literature.

No adverse effects on body weight, food and water consumption, mortality rate or the histology of the major organs that was due to exposure to 1,4-dichlorobenzene were observed in groups of 75 male and 75 female SPF Alderly Park Swiss strain mice exposed to 0, 75 or 500 ppm (0, 450 or 3000 mg/m^3) of 1,4-dichlorobenzene, 5 hours/day, 5 days/week for 57 weeks (Loeser and Litchfield, 1983). The females were observed for an additional

19 weeks after the end of treatment, but the males were killed at the end of the treatment period because of the large number of males (80%) that died from fighting and respiratory infections.

No treatment-related effects on body weight, food or water consumption, mortality rate, blood biochemistry hematology or the histology of the major organs were observed in groups of 76-79 male and 76-79 female Alderly Park Wistar-derived rats exposed to 0, 75 or 500 ppm (0, 450 or 3000 mg/m³) of 1,4-dichlorobenzene, 5 hours/day, 5 days/week for 76 weeks (Loeser and Litchfield, 1983). The rats of both sexes were observed for an additional 36 weeks after the last exposure. The endpoints evaluated included body and organ weights, clinical chemistry, hematology, urinalysis and histology of the major organs. At the 500 ppm exposure level, increased liver and kidney weights accompanied by "slightly" elevated urinary coproporphyrin levels were reported. Histopathological lesions were not observed in the liver or kidney at either dose tested. "Small" increases in the heart and lung weight unaccompanied by any histological alteration were reported in the rats exposed to 500 ppm of 1,4-dichlorobenzene. "Some suggestions of increased liver weights" were reported in the rats exposed to 75 ppm, but the authors concluded that no adverse effects were observed in the rats exposed to 75 ppm.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding the teratogenic or reproductive effects of oral exposure to 1,2-dichlorobenzene, 1,3-dichlorobenzene or 1,4-dichlorobenzene could not be located in the available literature.

3.3.2. Inhalation. Groups of ~30 pregnant F344 rats and ~30 pregnant New Zealand white rabbits were exposed to 0, 100, 200 or 400 ppm (0, 600, 1200 or 2400 mg/m³) of 1,2-dichlorobenzene, 6 hours/day on days 6-15 (rats) or

days 6-18 (rabbits) of gestation (Hayes et al., 1985). Endpoints evaluated included maternal and fetal body weights, maternal organ weights, number of litters/groups, number of fetuses/litter, number of resorptions/litter, number of litters with resorptions, and the incidence of visceral and skeletal malformations. Maternal body weight gain was significantly depressed in all groups of rats exposed to 1,2-dichlorobenzene. Relative and absolute liver weight was significantly increased in the dams exposed to 400 ppm; only relative liver weight was significantly increased in the dams exposed to 100 ppm. No adverse effects were observed in the rabbit dams, and no teratogenic or adverse developmental effects were observed in either the rats or the rabbits.

Pertinent data regarding the teratogenic or other reproductive effects of inhaled 1,3-dichlorobenzene could not be located in the available literature.

Loeser and Litchfield (1983) summarized a report by Hodge et al. (1977) in which groups of 20 pregnant SPF rats were exposed to 0, 75, 200 or 500 ppm (0, 450, 1200 or 3000 mg/m^3) of 1,4-dichlorobenzene for 6 hours/day on days 6-15 of gestation. Endpoints evaluated included maternal organ weights, maternal and fetal body weight, number of viable fetuses, number of resorptions and the incidence of visceral and skeletal malformations. There was no evidence of maternal toxicity. One fetus in each group was reported to have a malformation. No significant teratogenic, embryo or fetotoxic effects were associated with inhalation exposure to 1,4-dichlorobenzene in rats.

Groups of 29 or 30 pregnant New Zealand rabbits were exposed to 0, 100, 300 or 800 ppm (0, 600, 1800 or 4800 mg/m^3) of 1,4-dichlorobenzene for 6 hours/day on days 6-18 of gestation (Hayes et al., 1985). Endpoints

evaluated included maternal organ weights, maternal and fetal body weights, number of implantation sites, resorptions and viable fetuses and the incidence of visceral and skeletal malformations. No significant teratogenic, embryo or fetotoxic effects were associated with inhalation exposure to 1,4-dichlorobenzene in rabbits.

The U.S. EPA (1983c) has decided to require no further teratogenicity testing of the dichlorobenzenes.

3.4. TOXICANT INTERACTIONS

As reviewed by U.S. EPA (1980a, 1985a), the dichlorobenzenes as a class have been reported to induce hepatic xenobiotic metabolizing enzymes. For example, oral administration of 1 mmol/kg of 1,4-dichlorobenzene in corn oil to male mice for 7 days decreased the toxicity of orally administered malathion, as indicated by an increased LD_{50} (Townsend and Carlson, 1981). 1,4-Dichlorobenzene, however, was not as potent as the trichlorinated benzenes in reducing the toxicity of some organophosphates (Townsend and Carlson, 1981). 1,3-Dichlorobenzene induced the hepatic enzyme, δ-ALA synthetase, in female rats treated by gavage for up to 5 days (Poland et al., 1971); however, ALA synthetase activity as well as serum levels of 1,3-dichlorobenzene decreased with increased duration of 1,3-dichlorobenzene treatment, indicating that 1,3-dichlorobenzene may stimulate its own metabolism (Poland et al., 1971). On the other hand, Reid et al. (1973) and Reid and Krishna (1973) reported that pretreatment of rats with phenobarbital increased the metabolism of subsequently administered 1,2-, 1,3- and 1,4-dichlorobenzene, whereas SKF525-A or piperonyl butoxide, microsomal enzyme inhibitors, decreased the metabolism of subsequently administered 1,2-, 1,3- and 1,4-dichlorobenzenes. All drugs were administered intraperitoneally in both studies (Reid et al., 1973; Reid and Krishna, 1973).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenicity of ingested 1,2-, 1,3- or 1,4-dichlorobenzene in humans could not be located in the available literature.

4.1.2. Inhalation. Pertinent quantitative data regarding the carcinogenicity of inhaled 1,2-, 1,3- or 1,4-dichlorobenzene in humans could not be located in the available literature. IARC (1982a) reported that five case histories described by Girard et al. (1969) suggest a possible association between leukemia and inhalation, and perhaps percutaneous, exposure to the dichlorobenzene isomers.

4.2. BIOASSAYS

4.2.1. Oral. Increased incidences of tumors were not observed in groups of 50 male and 50 female B6C3F1 mice or in groups of 50 male and 50 female F344/N rats treated by gavage with 0, 60 or 120 mg/kg/day of 1,2-dichlorobenzene in corn oil, 5 days/week for 103 weeks (NTP, 1985) (see Section 3.2.1.).

Pertinent data regarding the carcinogenicity of orally administered 1,3-dichlorobenzene could not be located in the available literature.

In the NTP (1986) bioassay described in Section 3.2.1., groups of 50 male and 50 female B6C3F1 mice and 50 female F344/N rats were treated by gavage with 0, 300 or 600 mg/kg/day of 1,4-dichlorobenzene in corn oil, 5 days/week for 103 weeks. Groups of 50 male F344/N rats were treated by gavage with 0, 150 or 300 mg/kg/day of 1,4-dichlorobenzene in corn oil, 5 days/week for 103 weeks (NTP, 1986). All rats and mice were killed ~1 week after the last treatment. Oral exposure to 1,4-dichlorobenzene significantly increased the incidence of hepatocellular adenomas and/or carcinomas in male and high dose female mice (Tables 4-1 and 4-2). The NTP (1986)

indicated that although the statistical significance of the increased incidence of thyroid follicular cell adenoma in males and adrenal pheochromocytomas in females was only marginally statistically significant, biological significance may be implied because of the increased incidence of hyperplasia observed in these organs and because thyroid tumors have been reported in male hamsters treated with a related compound hexachlorobenzene (Cabral et al., 1977).

In rats, oral exposure to 1,4-dichlorobenzene significantly increased the incidence of renal tubular cell adenocarcinoma (control, 1/50; low, 3/50; high, 7/50) and renal tubular cell adenoma or adenocarcinoma (control 1/50; low, 3/50; high, 8/50) in high dose males but not females. Although the incidence of mononuclear cell leukemia was significantly increased in the high-dose male rats but not females (control, 5/50, low, 7/50, high, 11/50 in water), the NTP (1986) concluded that the increase may not have been treatment-related because the incidence of mononuclear cell leukemia is variable and low in concurrent controls (10%) when compared with its incidence in historical vehicle (corn oil) controls (17%).

4.2.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled 1,2- or 1,3-dichlorobenzene could not be located in the available literature.

No treatment-related effect on the incidence of tumors was observed in groups of 75 female SPF, Alderly Park Swiss mice exposed to 0, 75 or 500 ppm (0, 450 or 3000 mg/m^3) of 1,4-dichlorobenzene, 5 hours/day, 5 days/week for 57 weeks and subsequently observed for an additional 19 weeks after the last treatment (Loeser and Litchfield, 1983) (see Section 3.2.2.). The male mice exposed to 0, 75 or 500 ppm of 1,4-dichlorobenzene 5 hours/day, 5 days/week were killed after 57 weeks because most (~80%) died during the treatment period from fighting or respiratory infections.

TABLE 4-1

Incidence of Neoplastic Lesions in Male Mice Treated by Gavage with 1,4-Dichlorobenzene[a]

Tumor Type	Incidence (mg/kg/day)		
	0	300	600
Hepatocellular adenoma	14/50	11/49	32/50
Hepatocellular carcinoma	5/50	12/49	16/50
Hepatocellular adenoma or carcinoma[b]	17/50	22/49	40/50
Hepatoblastoma	0/50	0/50	4/50[c]
Follicular cell adenoma (thyroid)	NS	NS	NS
Pheochromocytomas (benign or malignant, combined)	0/47	2/48	4/49

[a]Source: NTP, 1986

[b]Mice that had both hepatocellular adenoma and hepatocellular carcinoma were counted only once.

[c]All hepatoblastomas occurred in mice that also had hepatocellular carcinomas.

NS = Not statistically significant

TABLE 4-2

Incidence of Neoplastic Lesions in Female Mice Treated by Savage with 1,4-Dichlorobenzene[a]

Tumor Type	Incidence (mg/kg/day)		
	0	300	600
Hepatocellular adenoma	5/50	5/48	19/50
Hepatocellular carcinoma	10/50	6/48	21/50
Hepatocellular adenoma or carcinoma[b]	15/50	10/48	23/50
Hepatoblastoma	0/50	0/48	0/50
Follicular cell adenoma (thyroid)	0/48	0/45	3/46
Pheochromocytomas (benign or malignant, combined)	NS	NS	NS

[a]Source: NTP, 1986

[b]Mice that had both hepatocellular adenoma and hepatocellular carcinoma were counted only once.

NS = Not statistically significant

No treatment-related effect on the incidence of tumors was observed in groups of 76-79 male and 76-79 female Alderly Park Wistar-derived rats exposed to 0, 75 or 500 ppm (0, 450 or 3000 mg/m³) of 1,4-dichlorobenzene, 5 hours/day, 5 days/week for 76 weeks and subsequently observed for an additional 36 weeks after the last treatment (Loeser and Litchfield, 1983) (see Section 3.2.2.).

4.3. OTHER RELEVANT DATA

1,2-Dichlorobenzene was not mutagenic to Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 with or without metabolic activation (NTP, 1985). As summarized in U.S. EPA (1985a), other studies (Anderson et al., 1972; Lawlor et al., 1979) have reported that 1,2-dichlorobenzene is not mutagenic in S. typhimurium. An increased incidence of chromosomal aberrations, including single and double chromosome breaks, was reported in 8 male and 18 female humans accidentally exposed to vapors of 1,2-dichlorobenzene for four 8-hour workdays (Zapata-Gayon et al., 1982).

All three isomers of dichlorobenzene increased the frequency of back mutations in an auxotrophic strain of Aspergillus nidulans (U.S. EPA, 1985a).

1,4-Dichlorobenzene was not mutagenic to S. typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 with or without rat liver microsomal activation (Lawlor et al., 1979; NTP, 1986). In a review, Loeser and Litchfield (1983) reported that an unpublished study by Anderson (1976) also concluded that 1,4-dichlorobenzene was not mutagenic to S. typhimurium strains TA98, TA100, TA1535 and TA1538 with or without metabolic activation. 1,4-Dichlorobenzene did not increase the mutation frequency in cultivated L5178Y/TK$^{+/-}$ mouse lymphoma cells with or without metabolic activation, nor did it increase the frequency of sister-chromatid exchange or chromosomal aberrations in Chinese hamster ovary in vitro (NTP, 1986).

A dominant lethal study (Anderson and Hodge, 1976) reviewed by Loeser and Litchfield (1983) indicated that 1,4-dichlorobenzene was not mutagenic to the sperm cells of mice exposed to 75, 225 or 450 ppm of 1,4-dichlorobenzene for 6 hours/day for 5 days.

4.4. WEIGHT OF EVIDENCE

1,2-Dichlorobenzene has been classified as an IARC Group 3 and EPA Group D chemical based on inadequate evidence for carcinogenicity in humans, animals and short-term tests (U.S. EPA, 1985b). In the NTP (1985) study using 1,2-dichlorobenzene, survival rates were comparable for all groups except high-dose males: 19/50 vs. 42/50 in controls. Seventeen of the high-dose males were accidently killed by gavage procedures. Thus, we cannot conclude that survival was lower in any group of rats or mice. Body weights were not significantly affected in either species and treatment-related lesions were not detected. On this basis it would appear that the maximum tolerated dose was not reached and this study is therefore inadequate to fully assess carcinogenicity of 1,2-dichlorobenzene. Mutagenesis studies were limited and results in most but not all cases were negative. Therefore, based on the above evidence, 1,2-dichlorobenzene would be classified as a Group D chemical (U.S. EPA, 1986).

1,3-Dichlorobenzene has not been classified by IARC but belongs in IARC Group 3 (IARC, 1982b). 1,3-Dichlorobenzene is most appropriately placed in EPA Group D because its carcinogenicity in animals and humans has not been evaluated and therefore cannot be classified as to its carcinogenic potential (U.S. EPA, 1985b).

Based on the results of the NTP (1986) bioassay in which a significantly increased incidence in hepatocellular carcinoma or adenoma was observed in male and female B6C3F1 mice treated by gavage with 1,4-dichlorobenzene 5

days/week for 103 weeks and a significantly increased incidence in renal tubular cell carcinoma or adenoma was observed in male F344/N rats treated by gavage 5 days/week for 103 weeks, this chemical belongs in EPA Group B2 (U.S. EPA, 1986) and IARC Group 2B. EPA Group B2 chemicals are probable human carcinogens and include chemicals for which the evidence for carcinogenicity is adequate in animals but inadequate in humans. IARC Group 2B includes chemicals for which there is sufficient evidence of carcinogenicity in animals but inadequate carcinogenicity data for humans.

5. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1985, 1986) and OSHA (1985) has recommended a ceiling limit of 50 ppm (~300 mg/m³) for 1,2-dichlorobenzene to prevent serious eye and nasal irritation as well as headache, nausea and throat irritation. Absorption through the skin may contribute substantially to the body burden of an individual exposed to 1,2-dichlorobenzene (ACGIH, 1986). An ambient water quality criterion of 400 µg/ℓ was calculated for 1,2-dichlorobenzene based on an RfD of 0.94 mg/day derived from the NOEL of 18.8 mg/kg/day, 5 days/week in the 192-day gavage study by Hollingsworth et al. (1958). This criterion assumes the consumption of 2 ℓ of water and 6.5 g of fish/day.

A proposed drinking water guideline of 0.3 µg/ℓ was reported for 1,2-dichlorobenzene based on organoleptic considerations only (U.S. EPA, 1985b). A RMCL of 0.62 mg/ℓ was derived from an AADI of 0.09 mg/kg/day (3.12 mg/ℓ) for 1,2-dichlorobenzene, assuming consumption of 2 ℓ of water/day and a 20% contribution to total exposure from drinking water (U.S. EPA, 1985b). This determination was based on the NOAEL of 125 mg/kg, 5 days/week in the 13-week gavage study using rats and mice by NTP (1985).

The ACGIH (1985, 1986) has recommended a TLV-TWA of 75 ppm (~450 mg/m³), with a STEL of 110 ppm (~665 mg/m³), for 1,4-dichlorobenzene to protect against acute and chronic poisoning. OSHA (1985) reported an occupational standard of 75 ppm (~450 mg/m³) for 1,4-dichlorobenzene. An RfD of 0.013 mg/kg/day of 1,2-dichlorobenzene was derived by multiplying the NOAEL of 18.8 mg/kg/day from the Hollingsworth et al. (1956) study by 5/7 days and dividing by an uncertainty factor of 1000 (U.S. EPA, 1980a).

The U.S. EPA (1980a) derived an ambient water quality criterion of 400 µg/l based on an RfD of 0.94 mg/day (0.013 mg/kg/day) derived from the NOEL of 18.8 mg/kg in the 192-day study using rats by Hollingsworth et al. (1956).

The U.S. EPA (1980a) adopted the ambient water quality criterion of 400 µg/l derived for 1,2- and 1,4-dichlorobenzene as the criterion for 1,3-dichlorobenzene on the basis of "the similarity of toxicities among the DCB isomers."

The U.S. EPA (1985b) is considering the appropriateness of deriving drinking water regulatory criteria for 1,3-dichlorobenzene based on the toxicity data available for 1,2-dichlorobenzene.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). Two subchronic oral studies (Hollingsworth et al., 1958; NTP, 1985) were available from which to derive an RfD_{SO} for 1,2-dichlorobenzene. The U.S. EPA (1980a) derived an RfD of 0.94 mg/day, equivalent to 0.013 mg/kg/day, from the NOEL of 18.8 mg/kg/day in the 192-day rat gavage study by Hollingsworth et al. (1958). Because the rats were treated for 5 days/week, the dose of 18.8 mg/kg/day was converted to 13.4 mg/kg/day and multiplied by 5/7 days to correct for continuous exposure. The corresponding RfD_{SO} of 0.13 mg/kg/day (9.4 mg/day) can be derived from this dosage by application of an uncertainty factor of 100. In this experiment, only elevated liver and kidney weights, without evidence of histopathological lesions, were observed at 188 mg/kg the next highest dose tested.

More recent data suggest that an RfD_{SO} based on the NOEL of 18.8 mg/kg may be unnecessarily conservative. In the 13-week gavage study using rats and mice (NTP, 1985), the dose of 125 mg/kg 1,2-dichlorobenzene appeared to be a NOAEL in both species. Decreased relative spleen weight in female mice, the only effect in mice at this dose, occurred in all treated groups. No evidence of histopathological lesions were associated with this effect below 500 mg/kg. In rats, elevated liver weight was noted, accompanied by mild histopathological lesions of degeneration at 125 mg/kg; similar lesions were not observed at 188 mg/kg in the earlier Hollingsworth et al. (1958) study or at 120 mg/kg in the chronic NTP (1985) study using rats. The 125 mg/kg dose in the subchronic rat study (NTP, 1985) was selected by the U.S. EPA (1985b) as the basis for the RMCL for 1,2-dichlorobenzene and is regarded as the appropriate basis for the RfD_{SO}. Multiplication by 5/7

days to reflect treatment 5 days/week and application of an uncertainty factor of 100 results in an RfD_{SO} for 1,2-dichlorobenzene of 0.9 mg/kg/day or 63 mg/day for a 70 kg human.

Pertinent data regarding the subchronic oral toxicity of 1,3-dichlorobenzene could not be located in the available literature. The U.S. EPA (1980a) derived a water quality criterion for 1,3-dichlorobenzene by analogy to 1,2- and 1,4-dichlorobenzene. Since this derivation, the 1,4-isomer has been shown to be a carcinogen in both rats and mice (NTP, 1986). In a more recent analysis, the U.S. EPA (1985b) declined to promulgate drinking water regulations for the 1,3-isomer and questioned the appropriateness of deriving a criterion by analogy to the other isomers. No RfD_{SO} for 1,3-dichlorobenzene will be derived, pending a more adequate data base.

The results of the NTP (1986) bioassay in which 1,4-dichlorobenzene was associated with significantly increased liver tumors in male and female mice and significantly increased renal tumors in male rats (see Section 6.3.) preclude the derivation of an RfD_{SO} for 1,4-dichlorobenzene.

6.1.2. Inhalation (RfD_{SI}). Based on the study by Hollingsworth et al. (1958) in which groups of 7-8 male and 7-8 female guinea pigs and 16-20 male and 17-20 female rats were exposed to 0, 49 ppm (290 mg/m³) or 93 ppm (560 mg/m³) of 1,2-dichlorobenzene for 7 hours/day, 5 days/week for up to 7 months, the highest NOEL below which no effects were reported occurred in the rats exposed to 290 mg/m³. The higher dose caused significantly decreased body weight in the male rats and significantly decreased spleen weight unaccompanied by histological alteration in the male guinea pigs. A NOAEL of 44.2 mg/kg/day is estimated by multiplying the exposure dose (290 mg/m³) by 7/24 hours and 5/7 days and the daily reference inhalation volume of a rat of 0.223 m³/day (U.S. EPA, 1980b) and by dividing by the

experimentally reported final average rat body weight of 0.305 kg (290 x 5/7 x 7/24 x 0.223 x 1/0.305). The RfD_{SI} of 31 mg/day (0.44 mg/kg/day) is obtained by multiplying the NOEL of 44.2 mg/kg/day by the reference human body weight of 70 kg (U.S. EPA, 1980b) and by dividing by an uncertainty factor of 100 to account for interspecies extrapolation and the range of sensitivity within the human population to xenobiotics.

Pertinent data regarding the toxicity of 1,3-dichlorobenzene after subchronic inhalation could not be located in the available literature. For the reasons discussed in Section 6.1.1., an RfD_{SI} for the 1,3-isomer shall not be derived by analogy to the other dichlorobenzene isomers.

The results of the NTP (1986) bioassay in which 1,4-dichlorobenzene was associated with significantly increased liver tumors in male and female mice and significantly increased renal tumors in rats precludes the derivation of an RfD_{SI} for 1,4-dichlorobenzene.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_O). Two subchronic experiments, the Hollingsworth et al. (1958) study and the NTP (1985) study have been used to derive chronic oral RfDs for 1,2-dichlorobenzene. Based on the Hollingsworth et al. (1958) study, a NOEL of 18.8 mg/kg/day was identified. An RfD of 0.94 mg/kg for 1,2-dichlorobenzene was derived from this NOEL by the U.S. EPA (1980a). From the NTP (1985) experiment, the U.S. EPA (1985b) identified a NOAEL of 125 mg/kg and derived a provisional AADI of 3.12 mg/L, equivalent to 6.24 mg/day or 0.09 mg/kg/day.

Subsequent to these evaluations, the NTP (1985) conducted a 103-week gavage study using rats and mice in which there was a dose-related increased incidence of renal tubular regeneration in male B6C3F1 mice at 2 weeks

following gavage treatment with 60 or 120 mg/kg/day of 1,2-dichlorobenzene 5 days/week for 103 weeks. A NOAEL of 60 mg/kg/day was identified. A more appropriate RfD_0 can be derived from the chronic studies than from the subchronic studies, because the uncertainty associated with extrapolation from subchronic to chronic exposure is removed. An interim RfD_0 of 30 mg/day (0.43 mg/kg/day) is derived by multiplying the NOAEL of 60 mg/kg/day by 5/7 days and the reference human body weight of 70 kg (U.S. EPA, 1980b) and dividing by an uncertainty factor of 100 to account for interspecies extrapolation and the range of sensitivity to xenobiotics within the human population. This chemical is currently undergoing review by the RfD committee; therefore, this RfD is being recommended as an interim RfD_0 pending final verification.

The U.S. EPA (1983a) derived an RQ of 1000 for 1,2-dichlorobenzene (CS, 8.8; RV_e, 4; RV_d, 2.2) based on a LOAEL of 188 mg/kg/day associated with increased liver and kidney weights in female rats from the subchronic Hollingsworth et al. (1958) study.

Since the U.S. EPA (1983a) analysis, chronic data have become available that are a more appropriate basis for a CS based on chronic toxicity. A CS of 9 can be obtained from the LOAEL of 120 mg/kg/day from the NTP (1985) chronic study in which a significant increase in the incidence of renal tubular regeneration occurred in male mice treated by gavage with 120 mg/kg/day of 1,2-dichlorobenzene, 5 days/week for 103 weeks and killed 2 weeks after the last treatment. A human MED of 498 mg/day can be derived by multiplying the LOAEL of 120 mg/kg/day by 5/7 days, by the cube root of the ratio of the body weight of male mice (estimated at 0.04 kg from data provided by investigators) to that of reference man (70 kg) and by 70 kg to express the result in terms of mg/day for a 70 kg human. The MED of 498

mg/day is equivalent to an RV_d of 1.5. The effects in the kidney rate an RV_e of 6. The CS of 9 based on the chronic NTP (1985) study is more appropriate than the RQ based on the subchronic Hollingsworth et al. (1958) study.

Pertinent data regarding the toxicity of 1,3-dichlorobenzene after chronic oral exposure could not be located in the available literature and no RfD_0 is calculated for this isomer.

The results from the NTP (1986) bioassay in which groups of 50 male and 50 female B6C3F1 mice and F344/N rats were treated by gavage with 1,4-dichlorobenzene indicate that a significant increase in the incidence of hepatocellular carcinomas or adenomas in male and female mice and of renal tubular cell adenoma or adenocarcinoma in male rats is associated with the ingestion of 1,4-dichlorobenzene. Therefore, it is not appropriate to derive an RfD_0 or a chronic toxicity CS based on systemic toxicity of 1,4-dichlorobenzene. Although the U.S. EPA (1983b) reported an RQ of 1000 (CS, 9.0; RV_e, 5; RV_d, 1.8) for 1,4-dichlorobenzene based on the adverse liver effects observed after inhalation of 1,4-dichlorobenzene by rats, rabbits and guinea pigs (Hollingsworth et al., 1956), the RQ was derived before the completion of the NTP (1986) bioassay with 1,4-dichlorobenzene.

6.2.2. Inhalation (RfD_I). Pertinent data regarding the toxicity of 1,2-dichlorobenzene and 1,3-dichlorobenzene after chronic inhalation could not be located in the available literature. Lacking chronic data for 1,2-dichlorobenzene, a provisional RfD_I of 3.1 mg/day can be estimated by applying an additional uncertainty factor of 10 to the RfD_{SI} of 31 mg/day calculated from the subchronic study by Hollingsworth et al. (1958).

A CS of 10 can be calculated for inhalation exposure to 1,2-dichlorobenzene based on the depressed spleen weights in guinea pigs observed in the subchronic study by Hollingsworth et al. (1958); however, because of the uncertainties associated with subchronic to chronic extrapolation, this has not been done and the CS of 9 associated with renal tubular necrosis and regeneration in a chronic oral rat study is chosen to represent the toxicity associated with 1,2-dichlorobenzene.

The results of the NTP (1986) bioassay in which oral exposure to 1,4-dichlorobenzene was associated with significantly increased incidences of tumors in mice and rats preclude derivation of an RfD_I for 1,4-dichlorobenzene. Although no increase in the incidence of tumors was observed in the Loeser and Litchfield (1983) study in which groups of 76-79 male and 76-79 female Aderly Park Wister-derived rats exposed to 1,4-dichlorobenzene by inhalation, the demonstration of increased tumor incidences in mice and rats orally exposed to 1,4-dichlorobenzene requires that no RfD_I be derived unless the carcinogenicity of 1,4-dichlorobenzene can be demonstrated to be route specific. Currently, insufficient data are available to determine the effects of route of exposure on the carcinogenicity of 1,4-dichlorobenzene. Therefore, no RfD_I or chronic toxicity CS for 1,4-dichlorobenzene has been derived.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. No evidence of carcinogenicity was observed in male or female B6C3F1 mice or F344 rats treated with 60 or 120 mg/kg/day of 1,2-dichlorobenzene for 2 years (NTP, 1985).

Data regarding the carcinogenicity of 1,3-dichlorobenzene could not be located in the available literature.

1,4-Dichlorobenzene was associated with a significantly increased incidence of hepatocellular carcinoma or adenoma in male and female B6C3F1 mice and renal tubular cell adenoma or adenocarcinoma in male F344/N rats (NTP, 1986). Data used to calculate the q_1^* values are summarized in Tables 6-1, 6-2 and 6-3. The animal q_1^* was calculated using the incidence of animals surviving to the time of first tumor in the multistage model adapted by the U.S. EPA and updated by Howe and Crump (1982). The human q_1^* was derived by multiplying the animal q_1^* by the cube root of the ratio of the human to animal body weights and the ratio of the length of the experiment to the lifespan of the animal which, in this case, is 1 for both mice and rats. The q_1^*, 2.4×10^{-2} $(mg/kg/day)^{-1}$, is derived from the hepatocellular carcinoma or adenoma incidence data in the male mice and is selected as most stringently representing the oral carcinogenic potency of 1,4-dichlorobenzene to humans.

6.3.2. Inhalation. Pertinent data regarding the carcinogenicity of 1,2- and 1,3-dichlorobenzene after inhalation exposure could not be located in the available literature.

No increased incidence of tumors was observed in mice or rats exposed to 1,4-dichlorobenzene by inhalation for 57 or 76 weeks, respectively (Loeser and Litchfield, 1983). Data are not available from which to derive an inhalation q_1^* for 1,4-dichlorobenzene.

TABLE 6-1

Cancer Data Sheet for Derivation of q_1^*

Compound: 1,4-dichlorobenzene

Reference: NTP, 1986

Species/strain/sex: mice/B6C3F1/male

Route/vehicle: oral (gavage)/corn oil

Length of exposure (le) = 103 weeks

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Body weight = 0.042 kg (estimated from graphs)

Tumor site and type: hepatocellular carcinoma or adenoma

Exposure (mg/kg/day)	Transformed Dose† (mg/kg/day)	Incidence No. Responding/No. Tested
0	0	17/44
300	212.2	22/40
600	424.5	40/42

Unadjusted $q_1^* = 2.042 \times 10^{-3}$ $(mg/kg/day)^{-1}$

Human $q_1^* = 2.4 \times 10^{-2}$ $(mg/kg/day)^{-1}$

†Transformed dose obtained by multiplying exposure dose by 5/7 days and 103/104 weeks.

TABLE 6-2

Cancer Data Sheet for Derivation of q_1^*

Compound: 1,4-Dichlorobenzene

Reference: NTP, 1986

Species/strain/sex: mice/ B6C3F1/female

Route/vehicle: oral (gavage)/corn oil

Length of exposure (le) = 103 weeks

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Body weight = 0.033 kg (estimated from graphs)

Tumor site and type: hepatocellular carcinoma or adenoma

Exposure (mg/kg/day)	Transformed Dose[a] (mg/kg/day)	Incidence No. Responding/No. Tested
0	0	15/44[b]
600	424.5	36/44

Unadjusted $q_1^* = 4.434 \times 10^{-3}$ $(mg/kg/day)^{-1}$

Human $q_1^* = 5.697 \times 10^{-2}$ $(mg/kg/day)^{-1}$

[a]Transformed dose obtained by multiplying the exposure dose by 5/7 days and 103/104 weeks.

[b]Number of animals surviving to week of first tumor

TABLE 6-3

Cancer Data Sheet for Derivation of a q_1^*

Compound: 1,4-dichlorobenzene

Reference: NTP, 1986

Species/strain/sex: rats/F344/male

Route/vehicle: oral (gavage)/corn oil

Length of exposure (le) = 103 weeks

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Body weight = 0.475 kg (estimated from graphs)

Tumor site and type: renal tubular cell adenocarcinoma or adenoma

Exposure (mg/kg/day)	Transformed Dose† (mg/kg/day)	Incidence No. Responding/No. Tested
0	0	1/50
150	106.1	3/50
300	212.2	8/50

Unadjusted $q_1^* = 1.037x19^{-3}$ $(mg/kg/day)^{-1}$

Human $q_1^* = 5.47x10^{-3}$ $(mg/kg/day)^{-1}$

†Transformed dose obtained by multiplying exposure dose by 5/7 days and 103/104 weeks.

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APPENDIX A

Summary Table for 1,2-Dichlorobenzene

	Species	Experimental Exposure/Dose (mg/kg/day)	Effect	Reference Dose (RfD or RfD_S)	Reference
Inhalation					
RfD_{SI} (formerly AIS)	rat	290 mg/m³, 7 hours/day, 5 days/week for up to 7 months	no adverse effect	31 mg/day	Hollingsworth et al., 1958
RfD_I (formerly AIC)	rat	290 mg/m³, 7 hours/day, 5 days/week for up to 7 months	no adverse effect	3.1 mg/day	Hollingsworth et al., 1958
Oral					
RfD_{SO}	rat	125 mg/kg/day, 5 days/week for 13 weeks	no adverse effect	63 mg/day	NTP, 1985
RfD_O	rat	60 mg/kg/day, 5 days/week for 103 weeks	no adverse effect	30 mg/day	NTP, 1985
Maximum CS	mouse, male	120 mg/kg/day, 5 days/week for 103 weeks (RV_d = 1.5)	increased renal tubular regeneration in males (RV_e = 6)	CS=9	NTP, 1985

APPENDIX B

Summary Table for 1,4-Dichlorobenzene*

Route	Species	Experimental Exposure/Dose (mg/kg/day)	Effect	q_1^* or Unit Risk
Oral	mouse/ female	0, 300, 600 mg/kg/day, 5 days/week for 103 weeks (gavage)	increased incidence of hepatocellular carcinoma or adenoma	2.4×10^{-2} $(mg/kg/day)^{-1}$

*Source: NTP, 1986